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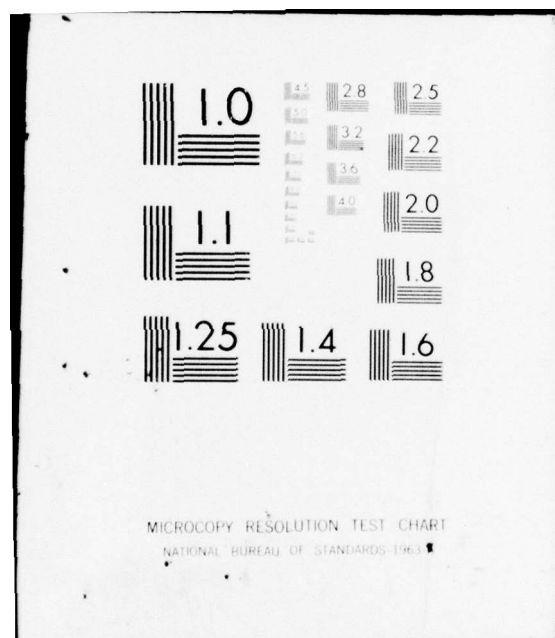
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EDGEWOOD ARSENAL TECHNICAL REPORT

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THIAMINE HYDROCHLORIDE AS AN ADJUNCT TO PRALIDOXIME
IN A SIMULATED THERAPEUTIC SETTING

by

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PREFACE

The work described in this report was authorized under Project/Task 1W762710AD2502, Medical Defense Against Chemical Agents, Prophylaxis and Therapy for Lethal Agents. This work was started in April 1974 and completed in May 1974.

The volunteers in these tests are enlisted US Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

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THIAMINE HYDROCHLORIDE AS AN ADJUNCT TO PRALIDOXIME IN A SIMULATED THERAPEUTIC SETTING

I. INTRODUCTION.

The recommended mode of administration of pralidoxime chloride (pyridine-2-aldoxime methochloride) used to reactivate the inhibited enzyme in anticholinesterase compound intoxication is by intravenous infusion over a 15- to 30-minute period.¹⁻³ Previous studies from this laboratory have demonstrated that thiamine hydrochloride, administered by intramuscular or intravenous infusion, significantly alters the disposition of pralidoxime by delaying renal excretion, prolonging plasma half-life, and increasing plasma concentrations of oxime given by rapid intravenous injection.^{4,*}

This study was undertaken to investigate the disposition of pralidoxime when given in the therapeutic manner recommended. We further attempted to study the alteration of oxime decay and excretion when thiamine was added to the infusion solution.

II. METHODS.

A. Subjects.

The subjects were five US Army enlisted personnel who agreed to participate in the study after thorough explanation and discussion. The subjects passed complete physical and laboratory examinations [chest X-ray, ECG, complete blood count, routine urinalysis, blood urea nitrogen, serum creatinine, and liver function tests (SGOT, alkaline phosphatase, serum bilirubin)]. A detailed history of allergy was obtained and subjects potentially hypersensitive to thiamine were excluded from the study.

B. Design.

Each man served as his own control. The subjects entered the ward on the evening before the study, ate a light breakfast about 1 hour before the test started, and drank 1 to 2 liters of fluid in the 2 hours preceding drug administration.

In the control trials, 1000 mg of pralidoxime chloride** in 250 ml of normal saline was infused into the antecubital vein over a 30-minute period. In the experimental trials, 200 mg of thiamine hydrochloride† was added to the above infusion mixture.

The trials were randomized and were performed over two successive 24-hour periods. After the infusion was started, urine from each subject was pooled for the following time periods: 0-1.5, 1.5-3.0, 3.0-6.0, and 6.0-24.0 hours. Blood was drawn through an indwelling scalp needle in the antecubital vein in the opposite arm, which was kept open with heparin, at 0.05, 0.10, 0.15, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, and 6.0 hours after the start of the infusion. Plasma and urine were analyzed for oxime by the method of Groff, *et al.*⁵

* Josselson, J., and Sidell, F. R. Unpublished data.

** Protopam, Ayerst Laboratories, Inc., New York, New York 10017.

† Thiamine Hydrochloride Injection, U.S.P., Natcon Chemical Co.

Blood pressure and heart rates were measured at 5-minute intervals for the first hour after the infusion was begun and at 30-minute intervals thereafter for 4 hours. Subjective responses to both thiamine and pralidoxime were noted. Subjects were kept in bed for the first 3 hours of testing; thereafter they were permitted to walk about.

C. Clearance Calculations.

Because the renal elimination of pralidoxime, and hence the plasma concentration of the drug, is the result of drug interaction in the kidneys, it did not seem appropriate to fit the plasma concentration versus time data to the usual single-drug decay curve as has been done previously.^{4,7} Therefore, the areas under the plasma concentration versus time curve (AUC) were estimated using the trapezoid (Simpson's) rule. The total areas under the curves (AUC_{∞}) were approximated using $AUC_{6 \text{ hr}}$ estimates. This method underestimated the AUC_{∞} to a greater extent for the thiamine trials than for control trials. Thus, the estimated plasma clearances are higher than the actual clearances. Therefore, significant differences in plasma clearance from control to thiamine trials similarly are underestimated.

From the AUC data, the plasma clearance (PC) and renal clearance (RC) of oxime were calculated using equation 1 and equation 2.

$$PC = D/AUC \quad (1)$$

$$RC = E_t/AUC_t \quad (2)$$

where D is the drug dose and E_t the amount of oxime excreted into the urine per unit time.

III. RESULTS.

A. Clinical Findings.

In the control trials, no changes were observed in blood pressures or in heart rates. Four of five subjects complained of transient visual phenomena (including visual blurring, diplopia, visual heaviness), never lasting more than 3 to 5 minutes.

During the thiamine trials, two of five subjects had increases in blood pressure, three of five showed increases in heart rates, and all subjects had mild side effects which seemed to be potentiated by the combination of vitamin and oxime.

Rises in systolic, diastolic, and mean arterial pressure were observed in two subjects. Such hypertensive changes have been described before with oxime, usually at doses above 25 mg/kg.¹ One subject, with resting baseline blood pressure in the range of 124-138/80 mm Hg (mean arterial pressure 98), had a maximum elevation in systolic pressure to 178 mm Hg, in diastolic pressure to 86 mm Hg, and in mean pressure to 115 mm Hg. The other had a control pressure of 116-124/64 mm Hg (mean 83) and a maximum rise of systolic pressure to 154 mm Hg, diastolic pressure to 88 mm Hg, with a mean of 105 mm Hg. Maximal elevation of blood pressure was a delayed occurrence and did not begin until the infusion had been terminated, peaking usually about 30 to 45 minutes after cessation of the infusion. No subject had objective or subjective signs or symptoms related to the acute rise in pressure. Hypotensive agents were not used.

Three subjects (including the two above) showed sharp increases in pulse rates, from 54-72 to 96, from 72 to 94, and from 72-84 to 108, usually within 30 minutes after infusion had been completed. Subjects did not complain of palpitations or awareness of the increase in pulse rate.

All subjects complained of the same visual side effects seen in the control setting, but the symptoms were more prominent and more persistent with thiamine, usually remaining for 1 to 2 hours. The visual signs were accompanied by marked diplopia in three subjects. Four of the five men complained of fatigue and drowsiness, symptoms attributed to both pralidoxime and thiamine hydrochloride in previous studies.^{1,3} Two subjects had vitamin gustatory sensations immediately after the infusion was begun.

Despite the above observations, all drugs appeared to be tolerated well by all subjects; and no major untoward side effects were noted.

B. Plasma Concentrations.

The mean plasma concentrations are plotted in figure 1. Following the start of the infusion, oxime concentrations in the thiamine-treated group were significantly higher than corresponding control values at all sampling intervals beyond the first 3 minutes (0.05 hours). Plasma oxime concentrations in the thiamine group remained above the 4- μ g/ml level for more than 3 hours, while they declined to below that level within 90 minutes in control subjects.

C. Urinary Excretion of Pralidoxime.

Contrary to most previous data,^{4,*} mean cumulative urinary excretion of oxime was lower in the thiamine-treated group in the 24-hour collection period (723 mg/24 hr) than in the control group (836 mg/24 hr) ($p < 0.02$, paired t test). In part, this may be explained by the loss of an aliquot of urine (a 3- to 6-hour specimen) from one subject, but a real change in distribution and metabolism of oxime cannot be excluded.

Nevertheless, over the first 6 hours of study, significantly less oxime was excreted into the urine of the thiamine-treated group than into that of the control group even when the slightly lower cumulative excretion of the former group is taken into consideration ($p < 0.001$, paired t test), and, as in prior studies, significantly more oxime appeared in the urine of the thiamine group over the last 18 hours than in the control group ($p < 0.05$, paired t test).

Despite the small discrepancy in urinary excretion between the two groups, the cumulative excretion for both groups compares favorably with data obtained from previous studies in this laboratory which showed that 70% to 90% of a parenteral dose of oxime is excreted by the kidneys.^{4,6,7}

Urinary excretion data are summarized in table 1.

* Josselson, J. and Sidell, F. R. Unpublished data.

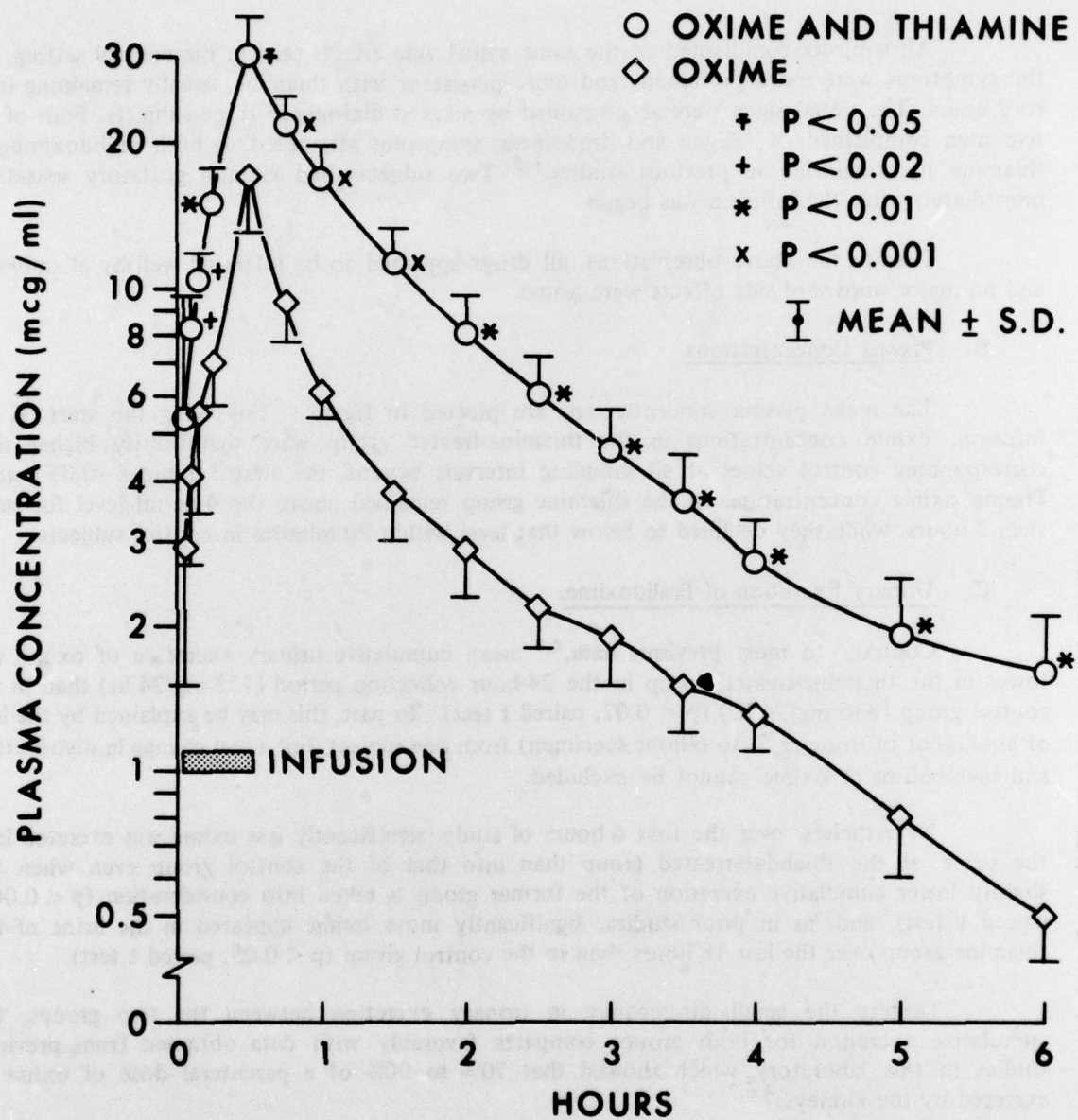


Figure. A Comparison of Mean Plasma Oxime Concentrations in Five Men After Pralidoxime Chloride Alone and Pralidoxime Chloride With Thiamine Hydrochloride

Table 1. Mean Urinary Excretion of Oxime in Five Subjects.

Time	Control	Thiamine	P
hr			
(a) Mean excretion of pralidoxime by aliquot (mg)			
0 - 1.5	610 ± 59	247 ± 35	<0.001
1.5 - 3	131 ± 27	150 ± 24	NS
3 - 6	68 ± 34	139 ± 70	NS
6 - 24	27 ± 12	188 ± 49	<0.01
0 - 24	836 ± 39	723 ± 72	<0.02
(b) Mean excretion of pralidoxime (% of total amount excreted)			
0 - 1.5	73 ± 5.6	34 ± 6.8	<0.001
1.5 - 3	16 ± 4.0	21 ± 5.4	NS
3 - 6	8 ± 4.1	19 ± 8.5	<0.05
6 - 24	3 ± 1.3	26 ± 5.4	<0.001
0 - 24	100	100	-

NS - not sufficient.

D. Clearance Data.

Clearance data are presented in table 2. Plasma and renal clearances were calculated from equation 1 and equation 2. There was almost a fourfold reduction in renal clearance from control values over the first 3 hours of the study when thiamine was concurrently administered with pralidoxime ($p < 0.005$, paired t test). Simultaneous creatinine clearance data showed no significant variation in clearance from control to thiamine trials. A correspondingly significant increase in the area under the plasma concentration versus time curve (AUC_{∞}), as estimated by the trapezoid rule, was also seen ($p < 0.005$, paired t test).

Plasma clearance of oxime demonstrated a 50% or greater reduction in all subjects following the addition of thiamine to the infusion solution ($p < 0.005$, paired t test).

IV. DISCUSSION.

Over the last decade, a large body of information has been acquired concerning pralidoxime chloride and its related congeners, their pharmacology, disposition, plasma decay, excretion, and pharmacokinetics.^{1,6-12} More recent investigations describe the alterations in oxime behavior produced by previous or simultaneous administrations of thiamine hydrochloride, a weak organic base believed to competitively inhibit the renal excretion of oxime.^{4,*}

The current study characterizes the behavior of pralidoxime when administered in one of the various methods recommended for the therapy of anticholinesterase intoxication. It does not apply in a situation where other changes in drug kinetics may occur as a result of heat and stress.⁹ The data are consistent with results obtained when oxime is given by rapid intravenous infusion. Furthermore, the changes which occur in plasma concentrations, delayed renal excretion, and drug clearance following simultaneous thiamine infusion are predictable on the basis of previous studies.^{4,*}

The decrease in the total amount of oxime excreted in the thiamine trials was not seen in earlier studies, suggesting the possibility that the increase in plasma half-life following thiamine may expose the oxime to alternate metabolic routes.

Of concern is the potentiation in two subjects of the hypertensive side effects of pralidoxime following administration of thiamine and the increase in chronotropy in three subjects. These changes were well tolerated in young, healthy volunteers, but may limit the usefulness of this combination in patients with a hypertensive history or borderline cardiovascular status.

The significant changes which occur in all of the parameters measured following thiamine infusion do not provide proof that such combination therapy will improve the clinical effectiveness of pralidoxime alone since no data are available to indicate optimal duration of therapeutic plasma levels of the oxime.

* Josselson, J. and Sidell, F. R. Unpublished data.

Table 2. Plasma Clearance of Pralidoxime Chloride in Five Subjects After Oxime Alone and Oxime in Combination with Thiamine Hydrochloride

Subject	AUC ₃		AUC ₆		RC ₃		PC*		Creat Cl	
	C	T	C	T	C	T	C	T	C	T
	$\frac{\text{mcg-min}}{\text{ml}}$		$\frac{\text{mcg-min}}{\text{ml}}$		ml/min		ml/min		ml/min	
R.D.	1123	2622	1269	2968	667	152	788	337	115	131
M.J.	938	1717	1052	1817	808	219	951	550	174	182
R.M.	1057	2519	1203	2956	642	126	831	338	123	133
C.P.	844	2574	962	2883	931	169	1040	347	157	135
B.R.	1052	2464	1213	2785	697	190	824	359	135	116
Mean	1003	2379	1140	2682	749	171	887	386	141	139
± S.D.	111	375	128	489	120	36	105	92	24	24
P	< .005		< .005		< .005		< .005		NS	

* Estimated using AUC₆ as an approximation of AUC_∞
n = 5

NS — not sufficient.

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